A longitudinal analysis of pneumococcal vaccine serotypes in pneumonia patients in Germany

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To the Editor:

Pneumococcal infections are globally the most frequent vaccine-preventable cause of death [1], and community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* is the main burden of pneumococcal disease in the elderly [2]. Since respiratory and blood cultures often remain negative in hospitalised patients with pneumococcal CAP due to prior antibiotic treatment, most cases are detected by the pneumococcal urinary antigen test (PUAT; BinaxNOW *S. pneumoniae*) [2, 3]. As the PUAT does not allow serotype discrimination, data on serotype distribution in adult non-bacteraemic pneumococcal CAP patients are sparse [4]. Pneumococcal conjugate vaccines (PCVs), which were primarily developed for vaccination of infants under 2 years of age, have significantly decreased invasive pneumococcal diseases worldwide in all age groups by herd protection effects [5, 6]. However, serotype replacement, *i.e.* replacement of vaccine serotypes by non-vaccine serotypes, has decreased the serotype coverage of PCVs over time [6, 7]. For Germany, we have described earlier the distribution of vaccine serotypes covered by the first but no longer available 7-valent pneumococcal conjugate vaccine (PCV7) and the 13-valent conjugate vaccine (PCV13) between 2002 and 2016 in adult patients with CAP enrolled into the prospective multicentre study CAPNETZ [8, 9]. PCV7 was replaced by either the 10-valent conjugate vaccine or, mainly, PCV13 in the German infant vaccination programme in 2010. However, PCV10 held the smallest market share of only 8% of pneumococcal vaccines in Germany in 2018 [10]. In adults, the German Standing Committee on Immunization (STIKO) recommends the 23-valent pneumococcal polysaccharide vaccine (PPV23) as routine pneumococcal vaccination for all adults of 60 years and above and for all patients with defined chronic comorbidities predisposing to pneumococcal disease, regardless of age. Moreover, since 2016, sequential vaccination with PCV13 followed by PPV23 is recommended for German adults at high risk for pneumococcal disease, including individuals with immunosuppression, chronic liver disease, chronic kidney disease and individuals with cerebrospinal fluid leaks or cochlear implants [11]. Recently, a 15-valent (PCV15) and a 20-valent conjugate vaccine (PCV20) have been licensed for the adult indication by the US Food and Drug Administration and are under evaluation by the European Medicines Agency [12, 13]. PCV15 contains all serotypes of PCV13 plus serotype 22F and 33F and PCV 20 includes PCV13 serotypes plus serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F.

The aim of the present study was to evaluate serotype distribution, secular trends and proportion of pneumonia caused by serotypes included in PCV13, PCV15, PCV20 and PPV23 among adult patients with all-cause CAP between 2013 and 2019. All patients enrolled in the CAPNETZ study in Germany between 1 January, 2013 and 31 December, 2019 with an available urine sample were included in the analysis. The CAPNETZ study (German Clinical Trials Register: DRKS00005274; approval number of leading ethics committee Medical Faculty of Otto-von-Guericke-University Magdeburg: 104/01; see acknowledgment or www.capnetz.de for participating centres) is a prospective observational multicentre cohort study of CAP patients treated in the hospital or in the outpatient setting. CAPNETZ inclusion criteria were age ⩾18 years, radiologically confirmed pneumonia, and at least one of the following clinical findings: cough, purulent sputum, fever or focal chest sign on auscultation. Exclusion criteria were hospitalisation during the 28 days preceding the study, immunosuppression and active tuberculosis [14]. All patients provided written informed consent prior to enrolment to the study. Urine samples of enrolled patients were prospectively collected and immediately treated with 0.5 M 1,4-piperazinediethanesulfonic acid buffer (Boston BioProducts) to a final concentration of 25 mM to stabilise respective polysaccharides.

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In Germany, the recently approved 20-valent pneumococcal conjugate vaccine had a substantially higher coverage against pneumonia in adults than the 13-valent vaccine, while the coverage gap compared to the 23-valent polysaccharide vaccine was small https://bit.ly/3q4skov

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Two serotype-specific urine antigen detection (UAD) assays [15, 16] covering different serotypes on urine samples were performed and analysed at Pfizer's Vaccines Research and Development Laboratory (Pearl River, NY, USA). The UAD assay is a limit assay that uses Luminex technology, with positivity cut-off limits (based on antigen concentrations read off a standard curve), established for each serotype using 400 control urine specimens collected from otherwise healthy adults without CAP. Using nonparametric tolerance intervals, the assay is set to achieve at least 97% specificity for each serotype. UAD1 covers PCV13 serotypes [14] and UAD2 covers 11 additional serotypes (the seven included in PCV20, *i.e.* ST8, ST10A, ST11A, ST12F, ST15B, ST22F and ST33F, and the four included in PPV23, *i.e.* ST2, ST9N, ST17F and ST20) [16]. UAD analyses were performed as described previously [15, 16]. Results were classified into "positive", "indeterminate" (excluded from analysis) and "negative". According to the STIKO recommendation for pneumococcal vaccination in adults, patients were classified as "at risk for pneumococcal disease" based on age ⩾60 years or on the presence of at least one comorbidity regardless of age [11]. We quantified the distribution of pneumococcal vaccine serotypes of PCV13, PCV15, PCV20 and PPV23 as absolute and relative frequencies (relative to the number of patients with information on the respective serotype). Furthermore, we applied logistic mixed regression modelling to assess annual trends (dependent variable: each of PCV13, PCV15, PCV20, PPV23 and serotype 3; independent variable: year

TABLE 1 Distribution of pneumococcal serotypes aggregated by pneumococcal vaccine formulation in patients with radiologically confirmed community-acquired pneumonia by UAD1/UAD2 by study period and in patient subgroups with STIKO recommendation for pneumococcal vaccination (individuals ⩾60 years and individuals 18–59 years with at-risk condition, *i.e.* ⩾1 comorbidity)

	Overall	Study period		
		2013–2014	2015–2017	2018–2019
⩾18 years of age				
Patients	1343	440	477	426
Any pneumococcal serotype detected by UAD1/UAD2	183 (13.7%)	61 (13.9%)	59 (12.4%)	63 (14.9%)
PCV13 serotypes	103 (7.7%)	33 (7.5%)	37 (7.8%)	33 (7.8%)
PCV15 serotypes	122 (9.1%)	43 (9.8%)	41 (8.6%)	38 (9.0%)
PCV20 serotypes	165 (12.3%)	58 (13.2%)	51 (10.7%)	56 (13.2%)
PPV23 serotypes	178 (13.3%)	58 (13.2%)	58 (12.2%)	62 (14.7%)
First most prevalent serotype: ST3	49 (3.7%)	14 (3.2%)	23 (4.8%)	12 (2.8%)
Second most prevalent serotype: ST8	21 (1.6%)	4 (0.9%)	5 (1.1%)	12 (2.8%)
18–59 years with at-risk condition				
Patients	316	95	112	109
Any pneumococcal serotype detected by UAD1/UAD2	38 (12.1%)	8 (8.4%)	13 (11.7%)	17 (15.6%)
PCV13 serotypes	23 (7.3%)	4 (4.2%)	8 (7.2%)	11 (10.1%)
PCV15 serotypes	28 (8.9%)	5 (5.3%)	10 (9.0%)	13 (11.9%)
PCV20 serotypes	37 (11.7%)	8 (8.4%)	13 (11.7%)	16 (14.7%)
PPV23 serotypes	37 (11.8%)	8 (8.4%)	13 (11.8%)	16 (14.7%)
First most prevalent serotype: ST3	10 (3.2%)	3 (3.2%)	5 (4.5%)	2 (1.8%)
Second most prevalent serotype: ST8	7 (2.2%)	2 (2.1%)	2 (1.8%)	3 (2.8%)
⩾60 years of age				
Patients	792	259	269	264
Any pneumococcal serotype detected by UAD1/UAD2	113 (14.4%)	39 (15.1%)	35 (13.1%)	39 (15.0%)
PCV13 serotypes	61 (7.7%)	19 (7.3%)	23 (8.6%)	19 (7.2%)
PCV15 serotypes	74 (9.4%)	28 (10.8%)	25 (9.3%)	21 (8.0%)
PCV20 serotypes	99 (12.6%)	37 (14.3%)	29 (10.8%)	33 (12.6%)
PPV23 serotypes	110 (14.0%)	37 (14.3%)	34 (12.7%)	39 (15.0%)
First most prevalent serotype: ST3	33 (4.2%)	9 (3.5%)	14 (5.2%)	10 (3.8%)
Second most prevalent serotype: ST11A	10 (1.3%)	4 (1.6%)	3 (1.1%)	3 (1.1%)

In seven patients, more than one individual serotype was identified. Information is missing on PCV13 serotypes in two patients (one from 2017, one from 2019), on PCV15 serotypes in five patients (one from 2013, one from 2017, three from 2019), on PCV20 serotypes in five patients (one from 2016, one from 2017, three from 2019), on PPV23 serotypes in seven patients (one from 2016, two from 2017, four from 2019), on ST3 in one patient (2017), and on ST8 and on ST11A in five patients (one from 2014, one from 2015, one from 2016, two from 2019) each. Percentages refer to number of patients with available information. At-risk condition refers one or more chronic comorbidities predisposing to pneumococcal disease, as defined by STIKO. UAD: urinary antigen detection test; STIKO: German Standing Committee on Immunization; PCV: pneumococcal conjugate vaccine; PPV: pneumococcal polysaccharide vaccine; ST: serotype.

of CAP acquisition; random effect (intercept): study centre; reported results: odds ratio with 95% confidence interval).

Out of 1831 patients screened, urine samples with a valid UAD test result were available for 1343 patients (73.3%) who were enrolled by 26 CAPNETZ centres distributed widely over Germany. Among these patients, 829 patients (61.7%) were male, 792 patients (59.0%) were aged ⩾60 years, 1038 patients (77.3%) had at least one comorbidity, and 1204 patients (89.7%) were treated in the hospital. Among the 1108 patients at risk for pneumococcal disease, only 179 patients (16.2%) reported any pneumococcal vaccination within the previous 5 years. In the overall study population during the study period 2013 to 2019, 183 of 1343 (13.6%) patients had a positive UAD1/2 test result. The most common vaccine serotypes were serotype 3 (n=49; 3.7% of all-cause CAP), followed by serotype 8 (n=21; 1.6% of all-cause CAP), serotype 22F (n=13; 1.0% of all-cause CAP) and serotype 11A (n=11; 0.8% of all-cause CAP). As shown in table 1, the overall proportion of vaccine-type pneumonia among all-cause pneumonia for PCV13, PCV15, PCV20 and PPV23 was 7.7% (n=103), 9.1% (n=122), 12.3% (n=165) and 13.3% (n=178), respectively. When regarding only pneumococcal pneumonia diagnosed by conventional diagnostics (PUAT or blood culture; n=74), PCV13, PCV15, PCV20 and PPV23 coverage was 37.8% (n=28), 44.6% (n=33), 64.9% (n=48) and 66.2% (n=49), respectively. Bacteraemic pneumococcal CAP was detected in 19 (2.1%) of the 889 patients for whom blood cultures were obtained. Among them, bacteraemic pneumococcal CAP was caused by serotype 8 in four patients (21.1%), serotype 4 and serotype 7F in two patients (10.5%), and serotype 3, serotype 12F, serotype 14, serotype 20 and serotype 33F in one patient (5.3%) each. The coverage of PCV13, PCV15, PCV20 and PPV23 in patients with bacteraemic CAP was 31.6% (n=6), 36.8% (n=7), 63.2% (n=12), and 68.4% (n=13). Over the entire observation period, we did not observe evidence for significant annual trends in pneumococcal vaccine serotype coverage (serotype 3: OR 0.95, 95% CI 0.81–1.10; PCV13: OR 0.94, 95% CI 0.83–1.05; PCV15: OR 0.93, 95% CI 0.84–1.03, PCV20: OR 0.95, 95% CI 0.86–1.04; PPV23: OR 0.99, 95% CI 0.90–1.08). Table 1 provides the serotype proportions of all-cause CAP for three time periods (2013–2014, 2015–2017 and 2018–2019) and the serotype proportion stratified by the above mentioned two STIKO classifications for patients "at risk" for pneumococcal disease (age ⩾60 years or patients 18–59 years with ⩾1 comorbidity). Serotype 3 was the most prevalent serotype in both patient subgroups, while the second most prevalent serotype was serotype 8 in patients 18–59 years with at-risk condition and serotype 11A in patients ⩾60 years.

In conclusion, PCV20 had a substantially higher coverage of all-cause CAP in adults compared to PCV13 (11.7% *versus* 7.3% for age group 18–59 years with ⩾1 comorbidity and 12.6% *versus* 7.7% for age group ⩾60 years). Our data show: 1) no decline of PCV13 serotypes in all-cause CAP between 2013–2019 mainly due to a persistently high proportion of serotype 3, suggesting no meaningful effect of childhood PCV13 vaccination on PCV13 coverage in pneumonia in adults during this time period; and 2) that the gap in the coverage between PCV20 and PPV23 was small and did not increase over the entire observation time. The presented data may be of use for modelling impact of pneumococcal vaccines and may contribute to informed decision-making of vaccination committees.

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